REMARKS

Claims 1-31 are pending in the present application. Claims 1-31 are rejected under 35 U.S.C. §103(a). Claims 9-11, 13, 14 and 17-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting. Applicants respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of the amendments and remarks below.

The Invention

The present invention provides novel condensation drug aerosols and methods for producing such aerosols. These condensations aerosols have little or no pyrolysis degradation products. The unique method for generating or producing such aerosols employs rapid vaporization of the drug to minimize drug degradation during the process. These vaporized drugs are subsequently condensed to form particles of a desirable particle size for inhalation. These aerosols are especially useful in the treatment of acute or chronic conditions wherein rapid onset of treatment is desirable.

The Amendments to the Specification

The abstract of the disclosure has been amended so that it is in compliance with word limit set forth in M.P.E.P. § 608.01(b).

The specification has been amended at ¶ **[0006]** to set forth language from the second full paragraph on page 2 and the last full paragraph on page 3 of U.S Provisional Application Serial No. 60/429,123, entitled "Delivery of a Diuretic through an Inhalation Route" filed on November 26, 2002, the entirety of which was incorported by reference (see ¶ **[0001]**).

The specification has also been amended at ¶¶ **[0098], [0100]-[0101], [0103]-[0106]** such that the trademark TEFLON® is capitalized and accompanied by the generic terminology.

No new matter is introduced by these amendments to the specification. The Examiner is respectfully requested to enter the amendments to the specification.

The Amendments to the Claims

Without prejudice to the Applicants' rights to present claims of equal scope in a timely filed continuing application, to expedite prosecution and issuance of the application, the Applicants have cancelled Claims 1-31 and presented new Claims 32-130. The new claims are supported throughout the specification.

The new claims do not introduce new matter. Applicants respectfully submit that the new claims put the case in condition for allowance. The Examiner is respectfully requested to enter the amendments to the claims and allow all of the claims.

The Rejection under 35 U.S.C. §103(a)

The Examiner rejected Claims 1-31 under 35 U.S.C. §103(a) as being unpatentable over Venkataraman (US 2001/0039262 A1) in view of Bartus et al. (U.S. Patent No. 6,514,482) in further view of Byron (US 2004/0016427 A1). In support of this rejection, the Office Action states that Venkataraman teaches treatment with diuretics, including ethacrynic acid, furosemide and bumetanide, provides effective symptomatic relief of congestive symptoms of heart failure, such as edema in the lower parts of the body. Office Action at 5. The Office Action further states that Venkataraman teaches both injectable and noninvasive routes for delivery of diuretics, including oral, nasal and pulmonary routes. *Id.* at 6. The Office Action concludes, "Venkataraman implicitly suggests the pulmonary administration by inhalation of diuretics." *Id.* at 7.

The Office Action acknowledges that Venkataraman "lacks an explicit teaching of administration by inhalation .... [and] also lacks the teaching of an aerodynamic diameter range and a C_{max} in 10 minutes or less after administration of the aerosol, the administration of condensation aerosols, and particle size." *Id.* However, the Office Action states that Bartus teaches teaches a method of pulmonary delivery of a medicament to a patient's respiratory tract, particles having an mass median aerodynamic diameter (MMAD) between 1 and 5 microns, and the achievement of optimal therapeutic concentration in less than 10 minutes. *Id.* The Office Action further states that Byron teaches the formation of aerosols by supplying a material in liquid form to a flow passage and heating the flow passage such that the material volatizes and expands out of an open end of the flow passage. The volatized material combines with ambient air such that the volatized material condenses to form the aerosol. *Id.* at 8.

The Office Action states that it "would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Venkataraman and Bartus to obtain pharmaceutically acceptable diuretic condensation aerosols, because the pulmonary route of administration of a therapeutic agent suggested by Venkataraman implies the inhalation of said agent through either the nose or the mouth; and Bartus teaches the pulmonary administration of medicaments via inhalation." *Id.* at 9. The Office Action goes on to state that "[a] person of ordinary skill would have been motivated to use Byron's method of making condensation aerosols of the composition resulting from the combination of the teachings of Venkataraman and Bartus, because Byron teaches how to make condensation aerosols by heating and vaporizing a liquid drug formulation to obtain aerosol particles having average sizes of less than 5 microns .... [and] also teaches that his invented apparatus can be modified to obtain particles with optimized average sizes, preferably between 0.2 and 1 micron." *Id.*

Applicants respectfully disagree in view of the elements of the amended claims and the disclosures of Venkataraman, Bartus and Byron. Venkataraman is directed to compositions comprising a combination of at least two or more diuretic agents, and methods for administering such compositions for treating cardiac indications (Venkataraman at **[0018]**). Venkataraman mentions that the disclosed compositions can be administered by a number of noninvasive routes, including "pulmonary" (Venkataraman at **[0020]**). However, as acknowledged in the Office Action, Venkataraman lacks an explicit teaching of administration by inhalation and also lacks teaching of a mass median aerodynamic diameter (MMAD) range, the administration of condensation aerosols, and particle size" (Office Action at 7). In addition, Venkataraman does not disclose or suggest an aerosol particle formed as a condensate of a vaporized drug, nor the advantages obtained by such a condensation aerosol. Moreover, Venkataraman fails to disclose generating an aerosol charaterized by less than 10% drug degradation products from the vaporization process, and formation of an aerosol having an MMAD of less than 5 microns. Nor does Venkataraman disclose heating a thin film containing the drug, on a solid support. These elements are required by independent Claims 32, 51, 70, 83, 95 and 106.

Bartus does not cure the deficiencies of Venkataraman or make obvious in view of that reference how to accomplish these tasks. Bartus does not disclose a condensation aerosol. Rather, Bartus is directed to a method of delivering low tap density particles for the treatment of CNS disorders and in particular, Parkinson's disease, via dry power inhalers or metered dose

inhalers. Like Venkataraman, Bartus does not disclose or suggest an aerosol particle formed as a condensate of a vaporized drug, nor the advantages obtained by such a condensation aerosol. Additionally, Bartus lacks teachings on heating a thin film, containing the drug, on a on a solid support, to produce a vapor of the drug. Dry powder inhalers, metered dose inhalers, nebulizers or instillation techniques do not vaporize the drug and then form a condensate of the drug. Moreover, in Bartus there is no disclosure of how one would form such particles of an antiparkinsonian drug – or any other drug compound – to generate an aerosol characterized by less than 10% drug degradation products, or how to obtain aerosols having a MMAD of less than 5 microns when vaporizing the drug. These elements, which are not taught in Bartus or Venkataraman, are required by independent claims 32, 51, 70, 83, 95 and 106.

Byron does not cure the deficiencies of Venkataraman and Bartus or make obvious in view of those references how to accomplish these tasks. Contrary to what is stated in the Office Action, one of skill in the art would not be motivated "to use Byron's method of making condensation aerosols of the compositions resulting from the combination of the teachings of Benkataraman and Bartus." Bartus states that larger, low density particles aerosolize more efficiently and avoid phagocytic engulfment by alveolar macrophages more effectively than smaller, denser aerosol particles. Bartus col. 13, lines 61-64.

> "The aerodynamic diameter can be calculated to provide for maximum deposition within the lungs. Previously this was achieved by the use of very small particles of less than about five microns in diameter, preferably between about one to about three microns, which are then subject to phagocytosis. Selection of particles which have a larger diameter, but which are sufficiently light (hence the characterization "aerodynamically light"), results in an equivalent delivery to the lungs, but the larger size particles are not phagocytosed. Improved delivery can be obtained by using particles with a rough or uneven surface relative to those with a smooth surface" (Bartus col. 13, line 65 to col. 14, line 7).

As pointed out in the Office Action, the aerosols generated by the device of Byron typically have a mass median particle diameter of less than 2 microns (Bartus at ¶ **[0074]**), while Bartus teaches that the preferred size range of particles is at least about 5 microns, preferably between about 5 microns and 30 microns. See, e.g., Bartus at col. 12, lines 60-66; col. 14, lines 12-14. Thus, Bartus teaches away from delivering its compositions using the device of Byron

Moreover, one of skill in the art would not have a reasonable expectation that the device of Byron would successfully form condensation aerosols suitable for inhalation that are characterized by less than 10% drug degradation products and an MMAD of less than 5 microns from the compositions resulting from the combination of Venkataraman and Bartus. For instance, under the method of Byron, the compositions resulting from the combination of Venkataraman and Bartus ("solid component") would have to be put into liquid form by combining with a "liquid component" (Byron at ¶ **[0076]**). However, Byron fails to provide specific guidelines for selecting an appropriate "liquid component" for a given drug ("solid component") or for predicting what effect heating the mixture will have on the solid component. This is further complicated when the solid component contains one or more additional component in addition to the drug, such as the surfactants, phospholipids, amino acids, etc., taught in Bartus (Bartus at col. 8, line 42 to col. 11, line 53) or the vehicles, carriers, recipients, binders, etc. taught by Venkataraman (e.g., Venkataraman at ¶ **[0018]**).

Finally, Byron does not teach or suggest all of the elements of independent Claims 32, 51, 70, 83, 95 and 106. Like Venkataraman and Bartus, Byron lacks specific disclosure on the presence of less than 10% degradation products. Furthermore, like Venkataraman and Bartus, Byron does not disclose or suggest heating a thin film, containing the drug, on a solid support. Thus, even if a skilled artisan "would have appreciated that aerosols are a preferred composition form for the administration of drugs via inhalation, as taught by Byron" (Office Action at 9), these references do not teach the skilled artisan how to make the condensation aerosol of the amended claims.

According to the MPEP § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations." Obviousness cannot be established by combining teachings in the prior art, absent some teaching or suggestion in the prior art that the combination be made (*In re Stencel* 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987); *In re Newell* 891 F. 2d 899, 13 USPQ2d 1248 (Fed. Cir. 1989)).

Byron does not cure the deficiencies of Bartus and Venkataraman. Accordingly, the Office Action fails to establish even a *prima facie* case of obviousness as each and every element of the invention is not taught or disclosed by these references. Moreover, as explained above, there would be no motivation to combine the teachings of Bartus and Venkataraman with the teachings of Byron to achieve the presently claimed invention. Even if the cited references were combined, the claimed invention would not result because Venkataraman, Bartus or Faithfull is not directed to heating a thin film containing a drug, on a solid support, or to forming condensation aerosols suitable for inhalation that are characterized by less than 10% drug degradation products and an MMAD of less than 5 microns.

Claims 33-50 which depend from Claim 32 are not obvious for the same reasons as Claim 32. Claims 52-69 which depend from Claim 51 are not obvious for the same reasons as Claim 51. Claims 71-82 which depend from Claim 70 are not obvious for the same reasons as Claim 70. Claims 84-94 which depend from Claim 83 are not obvious for the same reasons as Claim 83. Claims 96-105 which depend from Claim 95 are not obvious for the same reasons as Claim 95. Claims 107-130 which depend from Claim 106 are not obvious for the same reasons as Claim 106.

Accordingly, and in light of the foregoing arguments, the Applicants respectfully submit that these amendments put the case in condition for allowance and request that the Examiner reconsider and withdraw all rejections based on 35 U.S.C §103.

Double Patenting

Claim 9 was provisionally rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over Claim 12 of copending Application No. 10/057,197 (00014.01R) and Claim 28 of copending application No. 10/146,086.

Claims 9-11 were provisionally rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over Claims 12 and 18 of copending Application No. 10/633,876 (00060.01R) and Claims 15 and 21 of copending Application No. 10/633,877.

Claims 11, 13, 14 and 17-20 were provisionally rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over Claims 1, 2, 4, 74, 79 and 82 of copending Application No. 10/718,982 in view of Venkataraman (US2001/0039262 A1).

Claims 13 and 19 were provisionally rejected under the judicially created doctrine of

obvious-type double patenting as being unpatentable over Claims 1 and 19 of copending Application No. 10/768,205.

Applicants agree to file appropriate Terminal Disclaimers when patentable subject matter is detemined.

Conclusion

The Applicants appreciate the Examiner's careful and thorough review of the application and submit that the Examiner's concerns have been addressed by the amendments and remarks above. The Applicants accordingly request the Examiner to withdraw all rejections and allow the application. In the event the Examiner believes a telephonic discussion would expedite allowance or help to resolve outstanding issues, prosecution of the application, then the Examiner is invited to call the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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